UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/622,076	07/17/2003	**Rudolf Gilmanshin**	C0989.70054US00	1842

7590 12/10/2009

Helen C. Lockhart
Wolf, Greenfield & Sacks, P.C.
Federal Reserve Plaza
600 Atlantic Avenue
Boston, MA 02210

EXAMINER	
BERTAGNA, ANGELA MARIE	
ART UNIT	PAPER NUMBER
1637	
MAIL DATE	DELIVERY MODE
12/10/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/622,076	GILMANSHIN, RUDOLF	
	Examiner	Art Unit	
	Angela M. Bertagna	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 September 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5-7,9,11-15,17,19-21,24-34,68,91,125,126 and 128-130* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5-7,9,11-15,17,19-21,24-34,68,91,125,126 and 128-130* is/are rejected.

7)☒ Claim(s) *1,68,91,125 and 126* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/12/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

1. Applicant's response filed on September 4, 2009 is acknowledged. Claims 1, 2, 5-7, 9, 11-15, 17, 19-21, 24-34, 68, 91, 125, 126, and 128-130 are currently pending. In the response, Applicant amended claims 1, 11-15, 17, 68, 91, 125, 126, and 130. Claims 16, 22, and 23 were canceled.

The following include new grounds of rejection necessitated by Applicant's amendments to the claims. Any previously made rejections or objections not reiterated below have been withdrawn as being obviated by the amendment. Applicant's arguments filed on September 4, 2009 that remain pertinent to the new grounds of rejection below have been fully considered, but they were not persuasive for the reasons set forth in the "Response to Arguments" section. Accordingly, this Office Action is made **FINAL**.

Information Disclosure Statement

2. Applicant's submission of an Information Disclosure Statement on August 12, 2009 is acknowledged. A signed copy is enclosed.

Claim Objections

3. Claims 1, 68, 125, and 126 are objected to because of the following informalities: Replacing the phrase "is fluorescently labeled" in line 11 of claim 1, line 16 of claim 68, line 10 of claim 125, and line 13 of claim 126 with "are fluorescently labeled" is suggested to improve the grammar of the claim.

Claim 91 is objected to because of the following informalities: This claim appears to be missing the word "the" before the word "position" in line 8.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

5. Claim 129 is rejected under 35 U.S.C. 102(b) as being anticipated by Cheng et al. (Biochemical and Biophysical Research Communications (1991) 174(2): 785-789; cited previously).

Claim 129 is drawn to a method for analyzing a nucleic acid polymer. The method comprises providing a conjugate comprising a nucleic acid binding enzyme and a nucleic acid tag molecule, contacting the nucleic acid polymer with the conjugate, and determining a pattern of binding of the conjugate to the polymer that is not based on the catalytic activity of the enzyme. The nucleic acid binding enzyme binds non-specifically to the nucleic acid polymer, and the nucleic acid tag molecule binds specifically to the nucleic acid polymer. Also, the nucleic acid binding enzyme and the nucleic acid tag molecule are covalently linked.

Cheng analyzed the binding between HIV-1 reverse transcriptase and a primed nucleic acid template using UV cross-linking (see abstract and pages 786-787). The method disclosed by Cheng comprises analyzing a nucleic acid polymer (see page 786, last paragraph – page 787, first paragraph). Specifically, Cheng teaches combining a nucleic acid polymer (rA_{12-18}) with a nucleic acid tag molecule (dT_{10}) and a nucleic acid binding enzyme (HIV-1 reverse transcriptase) and performing UV cross-linking. This step results in "providing a conjugate comprising a nucleic acid binding enzyme and a nucleic acid tag molecule" and "contacting the conjugate with a nucleic acid polymer". The UV cross-linking step simultaneously provides a covalently bound conjugate comprising the nucleic acid tag molecule and the nucleic acid binding enzyme that contacts the nucleic acid polymer. When the reactants are combined in solution (page 786, last paragraph), the HIV-1 RT inherently binds non-specifically to and translocates along the nucleic acid polymer. Since the nucleic acid tag molecule (dT_{10}) is complementary to the nucleic acid polymer (rA_{12-18}), it binds in a sequence-specific manner to label the nucleic acid polymer. In the method of Cheng, the reverse transcriptase enzyme does not cleave the nucleic acid polymer. The analysis of the cross-linked complexes by electrophoresis (Figures 1 & 2) constitutes determining a binding pattern of the conjugate to the nucleic acid polymer. This determination is based on the detection of radioactive labels present on the nucleic acid polymer and the nucleic acid binding enzyme, and therefore, is not dependent on the catalytic activity of HIV-1 RT (see pages 786-787 and Figures 1-2). Finally, the HIV-1 RT taught by Cheng is a nuclease since it inherently possesses RNase H activity (page 785, 1st paragraph). Therefore, Cheng anticipates the method of claim 129.

6. Claim 91 is rejected under 35 U.S.C. 102(e) as being anticipated by Taira et al. (US 2003/0199471 A1; cited previously).

Claim 91 is drawn to a method for analyzing a nucleic acid molecule. The method comprises contacting the nucleic acid molecule with a conjugate comprising a nucleic acid binding enzyme and a nucleic acid tag molecule that are covalently linked to each another. The nucleic acid binding enzyme binds non-specifically to the nucleic acid molecule, whereas the nucleic acid tag molecule binds specifically to the nucleic acid molecule. The position of one or more conjugates when bound to nucleic acid molecule is then determined by a method that is not based on the catalytic activity of the nucleic acid binding enzyme.

Taira teaches a method for analyzing a nucleic acid molecule comprising: a first step of providing a conjugate comprising a nucleic acid tag molecule and a nucleic acid binding enzyme that are covalently linked to each other, a second step of contacting the nucleic acid polymer with the conjugate (see, for example, paragraphs 82, 85, & 86; see also paragraphs 31, 33, & 36), wherein the nucleic acid binding enzyme binds to the nucleic acid molecule non-specifically and translocates along the nucleic acid molecule (see paragraphs 33, 36-38, 82, 85, 86, and 128), and wherein the nucleic acid tag molecule binds to the nucleic acid molecule in a sequence-specific manner, thereby labeling the nucleic acid molecule (see paragraphs 31, 36-38, 85, 86, 106, and 128), and a third step of determining a pattern of binding of the conjugate to the nucleic acid polymer (paragraphs 36-38, 68, 85, 86, and 106). Determining the binding site of the nucleic acid tag molecule (*i.e.* the ribozyme) as described by Taira in paragraph 68, for example, constitutes determining (indirectly) the position of the conjugate when bound to the nucleic acid polymer as required by amended claim 91. Furthermore, in the method of Taira, the nucleic acid

binding enzyme (helicase) does not cleave or modify the nucleic acid molecule, nor is the helicase detected based on its catalytic activity.

7. Claim 91 is rejected under 35 U.S.C. 102(a) as being anticipated by Tahira et al. (JP 2001/190282 A; cited previously).

It is noted Taira et al. (US 2003/0199471 A1) is an English language equivalent of the above Japanese language document. The citations below refer to the English language document.

Claim 91 is drawn to a method for analyzing a nucleic acid molecule. The method comprises contacting the nucleic acid molecule with a conjugate comprising a nucleic acid binding enzyme and a nucleic acid tag molecule that are covalently linked to each another. The nucleic acid binding enzyme binds non-specifically to the nucleic acid molecule, whereas the nucleic acid tag molecule binds specifically to the nucleic acid molecule. The position of one or more conjugates when bound to nucleic acid molecule is then determined by a method that is not based on the catalytic activity of the nucleic acid binding enzyme.

Taira teaches a method for analyzing a nucleic acid molecule comprising: a first step of providing a conjugate comprising a nucleic acid tag molecule and a nucleic acid binding enzyme that are covalently linked to each other, a second step of contacting the nucleic acid polymer with the conjugate (see, for example, paragraphs 82, 85, & 86; see also paragraphs 31, 33, & 36), wherein the nucleic acid binding enzyme binds to the nucleic acid molecule non-specifically and translocates along the nucleic acid molecule (see paragraphs 33, 36-38, 82, 85, 86, and 128), and wherein the nucleic acid tag molecule binds to the nucleic acid molecule in a sequence-specific

manner, thereby labeling the nucleic acid molecule (see paragraphs 31, 36-38, 85, 86, 106, and 128), and a third step of determining a pattern of binding of the conjugate to the nucleic acid polymer (paragraphs 36-38, 68, 85, 86, and 106). Determining the binding site of the nucleic acid tag molecule (*i.e.* the ribozyme) as described by Taira in paragraph 68, for example, constitutes determining (indirectly) the position of the conjugate when bound to the nucleic acid polymer as required by amended claim 91. Furthermore, in the method of Taira, the nucleic acid binding enzyme (helicase) does not cleave or modify the nucleic acid molecule, nor is the helicase detected based on its catalytic activity.

.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 1, 2, 5, 6, 9, 11-13, 17, 24-31, 125, 126, 128, and 130 are rejected under 35 U.S.C. 103(a) as being unpatentable over Taira et al. (US 2003/0199471 A1; cited previously) in view of Daskis et al. (WO 2001/46467 A2; cited previously) and further in view of Thompson et al. (US 6,348,317 B1; cited previously).

These claims are drawn to a method for analyzing a nucleic acid polymer. The method comprises contacting the nucleic acid polymer with a conjugate comprising a nucleic acid binding enzyme and a nucleic acid tag molecule that are covalently linked to each another. The

nucleic acid binding enzyme binds non-specifically to the nucleic acid polymer, and the nucleic acid tag molecule binds specifically to the nucleic acid polymer. A pattern of the binding between the conjugate and the nucleic acid polymer is then determined using a backbone-specific label on the nucleic acid polymer. This determination is not based on the catalytic activity of the nucleic acid binding enzyme.

Regarding claims 1, 2, 12, 125, 126, 128, and 130, Taira teaches a method for analyzing a nucleic acid polymer comprising: a first step of providing a conjugate comprising a nucleic acid tag molecule and a nucleic acid binding enzyme that are covalently linked to each other, a second step of contacting the nucleic acid polymer with the conjugate (see, for example, paragraphs 82, 85, & 86; see also paragraphs 31, 33, & 36), wherein the nucleic acid binding enzyme binds to the nucleic acid polymer non-specifically and translocates along the nucleic acid polymer (see paragraphs 33, 36-38, 82, 85, 86, and 128), and wherein the nucleic acid tag molecule to bind to the nucleic acid polymer in a sequence-specific manner, thereby labeling the nucleic acid polymer (see paragraphs 31, 36-38, 85, 86, 106, and 128), and a third step of determining a pattern of binding of the conjugate to the nucleic acid polymer (paragraphs 36-38, 85, 86, and 106). In the method of Taira, the nucleic acid binding enzyme (helicase) does not cleave or modify the nucleic acid polymer, nor is the helicase detected based on its catalytic activity.

Regarding claims 5, 6, and 11, Taira teaches that the nucleic acid polymer is RNA, the nucleic acid tag molecule is RNA, and the nucleic acid binding enzyme is a helicase (paragraphs 43, 82, and 128). Taira further teaches that the nucleic acid polymer and the nucleic acid tag

molecule may be DNA at paragraph 23. Taira also teaches that the nucleic acid binding enzyme may be a DNA polymerase or an RNA polymerase at paragraph 22.

Regarding claim 9, Taira teaches that the nucleic acid tag molecule and the nucleic acid binding enzyme are conjugated using a linker molecule (paragraph 82).

Regarding claim 24, the mRNA target taught by Taira at paragraph 128 is not an *in vitro* amplified molecule.

Regarding claim 25, the ribozyme nucleic acid tag molecule taught by Taira at paragraph 128 is not an antisense molecule.

Regarding claim 26, Taira teaches ribozymes (nucleic acid tag molecules) that specifically bind to eukaryotic sequences (paragraph 64, for example).

Regarding claim 27, Taira teaches that the nucleic acid tag molecule is labeled with an agent, specifically the CTE region (paragraphs 82 and 128).

Regarding claim 31, Taira teaches detection of the ribozyme cleavage products, which results in indirect detection of the nucleic acid binding enzyme (paragraph 66).

Taira does not teach that the nucleic acid polymer is fluorescently labeled (*e.g.* with a backbone-specific label) as required by claims 1, 17, 125, 126, and 130. Taira also does not teach labeling the nucleic acid tag molecule and/or the nucleic acid binding enzyme with a fluorescent molecule as required by claims 1, 13, 125, 126, and 130, or that the nucleic acid tag molecule is labeled with a photocleaving agent as required by claims 28-30.

Daskis teaches a fluorescence-based method for detecting nucleic acid hybridization (see abstract and page 4, lines 4-25). Regarding claims 1, 13, 17, 125, 126, and 130, Daskis teaches detecting a target nucleic acid by hybridizing a nucleic acid probe to the target nucleic acid in the

presence of a fluorescent intercalating agent (*i.e.* a backbone-specific label) that may be covalently or non-covalently attached to the nucleic acid probe (see abstract, page 4, lines 4-25, and page 8, lines 16-24). Daskis teaches that the disclosed method permits rapid, sensitive, environmentally friendly, safe, and homogeneous monitoring of hybridization reactions (page 5, lines 1-7 and page 6, lines 7-25)

Regarding claims 28-30, as evidenced by Thompson, Daskis teaches fluorescent intercalating agents that are photocleaving agents (see page 8, lines 25-30 of Daskis and column 4, lines 3-25 and column 6, lines 1-31 of Thompson).

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to combine the teachings of Taira and Daskis. An ordinary artisan would have been motivated to label the nucleic acid tag molecule (*i.e.* the ribozyme) and the mRNA target molecule of Taira using the backbone-specific fluorescent intercalating agents taught by Daskis. An ordinary artisan would have been motivated to do so in order to obtain a rapid, sensitive, environmentally friendly, safe, and homogeneous method for analyzing the binding between the ribozyme-helicase conjugates of Taira and their mRNA targets. Thus, the methods of claims 1, 2, 5, 6, 9, 11-13, 17, 24-31, 125, 126, 128, and 130 are *prima facie* obvious over Taira in view of Daskis and further in view of Thompson.

10. Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over Taira et al. (US 2003/0199471 A1; cited previously) in view of Daskis et al. (WO 2001/46467 A2; cited previously) and further in view of Thompson et al. (US 6,348,317 B1; cited previously) and

further in view of McCall et al. (Proceedings of the National Academy of Sciences, USA (1992) 89(13): 5710-5714; newly cited).

Claim 7 is drawn to the method of claim 1, wherein the nucleic acid tag molecule is between 5 and 50 nucleotides in length.

The combined teachings of Taira, Daskis, and Thompson render obvious the methods of claims 1, 2, 5, 6, 9, 11-13, 17, 24-31, 125, 126, 128, and 130, as discussed above.

These references do not suggest the use of a nucleic acid tag molecule having a length within the claimed range.

McCall analyzed the minimal sequence requirements for activity of the hammerhead ribozyme (see abstract and page 5710). McCall teaches that the hammerhead ribozyme retains cleavage activity after truncation to 22 nucleotides (page 5712) and that the smaller, truncated ribozymes can be synthesized more easily and with less expense compared to their longer counterparts (page 5710).

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to utilize a ribozyme as the nucleic acid tag molecule having a length within the claimed range when practicing the methods resulting from the combined teachings of Taira, Daskis, and Thompson. An ordinary artisan would have been motivated to do so with a reasonable expectation of success, since McCall taught that the hammerhead ribozyme retains cleavage activity after truncation to 22 nucleotides (page 5712) and that the smaller, truncated ribozymes can be synthesized more easily and with less expense compared to their longer counterparts (page 5710). Thus, the method of claim 7 is *prima facie* obvious over Taira in view of Daskis and further in view of Thompson and further in view of McCall.

11. Claims 14 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Taira et al. (US 2003/0199471 A1; cited previously) in view of Daskis et al. (WO 2001/46467 A2; cited previously) and further in view of Thompson et al. (US 6,348,317 B1; cited previously) and further in view of Yamane (Nucleic Acids Symposium Series (2000) 44: 297-298).

Claims 14 and 15 are drawn to the method of claim 1, wherein the nucleic acid binding enzyme is fluorescently labeled and wherein the nucleic acid binding enzyme and the nucleic acid tag molecule are fluorescently labeled, respectively.

The combined teachings of Taira, Daskis, and Thompson render obvious the methods of claims 1, 2, 5, 6, 9, 11-13, 17, 24-31, 125, 126, 128, and 130, as discussed above.

These references do not suggest labeling the nucleic acid binding enzyme (helicase) in addition to the nucleic acid tag molecule and the nucleic acid polymer as required by claims 14 and 15.

Yamane teaches "smart probes", which are oligonucleotide probes labeled with a fluorophore and an intercalator (see abstract and Figure 1). Yamane teaches that fluorescence of the fluorophore is quenched when the probe is not hybridized to a complementary nucleic acid, and that this quenching is eliminated upon hybridization of the probe to a complementary nucleic acid (see Figure 1 and pages 297-298).

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to apply the teachings of Yamane to the methods resulting from the combined teachings of Taira, Daskis, and Thompson. Specifically, an ordinary artisan would have been motivated to utilize a doubly labeled helicase-ribozyme conjugate when practicing the methods resulting from the combined teachings of Taira, Daskis, and Thompson in order to obtain the

ability to only detect the conjugate when it has specifically bound to the target RNA. An ordinary artisan also would have recognized from the teachings of Yamane that the placement of the two labels on the conjugate (*i.e.* both labels on the nucleic acid tag molecule or one label on the helicase and one label on the nucleic acid tag molecule) was a matter of design choice, provided that the fluorescence of the fluorophore is quenched in the absence of specific binding. Therefore, an ordinary artisan would have been motivated to select either alternative with a reasonable expectation of success. Thus, the methods of claims 14 and 15 are *prima facie* obvious in view of the combined teachings of Taira, Daskis, Thompson, and Yamane.

12. Claims 19, 20, 33, 34, and 68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Taira et al. (US 2003/0199471 A1; cited previously) in view of Daskis et al. (WO 2001/46467 A2; cited previously) and further in view of Thompson et al. (US 6,348,317 B1; cited previously) and further in view of in view of Tegenfeldt et al. (WO 00/09757; cited previously).

Claims 19, 20, 33, and 34 are drawn to the method of claim 1, wherein a single molecule linear polymer analysis system is used to determine a pattern of binding of the enzyme-nucleic acid conjugate to the nucleic acid polymer. Claim 68 is drawn to a method for analyzing a nucleic acid polymer comprising binding a covalently-linked conjugate comprising a nucleic acid tag molecule and a nucleic acid binding enzyme to a nucleic acid polymer and analyzing the binding using a linear polymer analysis system.

The combined teachings of Taira, Daskis, and Thompson render obvious the methods of claims 1, 2, 5, 6, 9, 11-13, 17, 24-31, 125, 126, 128, and 130, as discussed above.

Regarding claim 68, Taira teaches a method for analyzing a nucleic acid polymer comprising: a first step of providing a conjugate comprising a nucleic acid tag molecule and a nucleic acid binding enzyme that are covalently linked to each other and a second step of contacting the nucleic acid polymer with the conjugate (see, for example, paragraphs 82, 85, & 86; see also paragraphs 31, 33, & 36), wherein the nucleic acid binding enzyme binds to the nucleic acid polymer non-specifically and translocates along the polymer (see paragraphs 33, 36-38, 82, 85, 86, and 128), and wherein the nucleic acid tag molecule to bind to the nucleic acid polymer in a sequence-specific manner, thereby labeling the nucleic acid polymer (see paragraphs 31, 36-38, 85, 86, 106, and 128), and a third step of determining a pattern of binding of the conjugate to the nucleic acid polymer (paragraphs 36-38, 85, 86, and 106). In the method of Taira, the nucleic acid binding enzyme (helicase) does not cleave or modify the nucleic acid polymer, nor is the helicase detected based on its catalytic activity.

Further regarding claim 68, as discussed above, the combined teachings of Taira, Daskis, and Thompson suggest labeling the nucleic acid polymer and the nucleic acid tag molecule with a fluorescent label.

The combined teachings of Taira, Daskis, and Thompson do not teach the use of a single molecule linear polymer analysis system as required by claims 19, 20, 33, 34, and 68.

Tegenfeldt teaches a linear polymer analysis system for optically analyzing polymers. Tegenfeldt teaches that the system is useful for performing a sequencing application wherein a nucleic acid is labeled with a fluorescent or radioactive label and subsequently exposed to an interaction station where the fluorescent/radioactive signal is detected (see pages 7-8, in particular the 1st full paragraph of page 8; see also claim 1).

Regarding claim 19, the system described by Tegenfeldt is a linear polymer analysis system (abstract).

Regarding claim 20, Tegenfeldt teaches that the system is useful for performing a sequencing application wherein a nucleic acid is labeled with a fluorescent or radioactive label and subsequently exposed to an interaction station where the fluorescent/radioactive signal is detected (see pages 7-8, in particular the 1st full paragraph of page 8; see also claim 1).

Regarding claim 33, the system described by Tegenfeldt is capable of analyzing single polymers (page 8).

Regarding claim 34, the system described by Tegenfeldt is an optical mapping system (page 7, line 33 – page 8, line 4).

Regarding claim 68, Tegenfeldt teaches a method (see page 9, lines 6-15) comprising (a) generating optical radiation of a known wavelength to produce a localized radiation spot, (b) passing a polymer through a microchannel, (c) irradiating the polymer at the localized spot, (d) sequentially detecting radiation resulting from interaction of the polymer with the optical radiation at the localized radiation spot, and (e) analyzing the polymer based on the detected radiation. Tegenfeldt teaches that the above method is useful for sequencing a nucleic acid molecule or expression mapping, stating, "Since generation of expression maps involve the sequencing and identification of cDNA or mRNA, more rapid sequencing necessarily means more rapid generation of multiple expression maps (page 2, lines 3-5)." Tegenfeldt also states, "The methods disclosed herein provide much longer read lengths than achieved by the prior art and a million-fold faster sequence reading (page 11, lines 13-14)."

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to use the detection system of Tegenfeldt to analyze the hybridization patterns produced by the method resulting from the combined teachings of Taira, Daskis, and Thompson. As noted above, Tegenfeldt expressly taught that the disclosed linear analysis system possessed several advantages compared to conventional detection methods, namely increased assay speed and the ability to analyze longer nucleic acid fragments (see page 2, lines 3-5 and page 11, lines 13-14). Since the methods of Taira were directed to determining ribozyme binding sites and identifying the target nucleic acids associated with particular phenotypes, an ordinary artisan would have been motivated to analyze the binding reactions of Taira using the single molecule linear polymer analysis system of Tegenfeldt in order to obtain a rapid and efficient detection method. An ordinary artisan would have also been motivated to utilize the linear polymer analysis method of Tegenfeldt, because its ability to detect single molecules (see page 8) would have increased the sensitivity of the method resulting from the combined teachings of Taira, Daskis, and Thompson. Since Tegenfeldt taught that the proposed read length is on the order of several hundred thousand nucleotides (see page 11), an ordinary artisan would have expected a reasonable level of success in analyzing the binding reactions of Taira using single molecule linear polymer analysis as taught by Tegenfeldt. Thus, the methods of claims 19, 20, 33, 34, and 68 are *prima facie* obvious in view of the combined teachings of Taira, Daskis, Thompson, and Tegenfeldt.

13. Claims 21 and 32 rejected under 35 U.S.C. 103(a) as being unpatentable over Taira et al. (US 2003/0199471 A1; cited previously) in view of Daskis et al. (WO 2001/46467 A2; cited previously) and further in view of Thompson et al. (US 6,348,317 B1; cited previously) and further in view of in view of Bertrand et al. (RNA (1997) 3: 75-88; cited previously).

Claim 21 is drawn to the method of claim 1, wherein the binding pattern is determined by fluorescence in situ hybridization (FISH). Claim 32 is drawn to the method of claim 31, wherein the nucleic acid binding enzyme is directed indirectly using an antibody that specifically binds thereto.

The combined teachings of Taira, Daskis, and Thompson render obvious the methods of claims 1, 2, 5, 6, 9, 11-13, 17, 24-31, 125, 126, 128, and 130, as discussed above.

Taira does not teach determining the binding pattern using FISH as required by claim 21. Taira also does not teach detecting the nucleic acid binding enzyme using an antibody that specifically binds thereto.

Bertrand teaches methods of controlling the intracellular localization of ribozymes (see abstract and page 76). Bertrand also teaches detecting the intracellular localization of the ribozymes using FISH (see Figure 5, pages 79-81, and page 87).

It would have been *prima facie* obvious to monitor the intracellular localization of the helicase-ribozyme conjugates of Taira using FISH. Since Taira taught using Northern blotting to monitor the intracellular localization of the ribozyme conjugates (see, for example, paragraphs 58, 62, 122-124, 145-146, 161, and 177-178), an ordinary artisan would have been motivated to substitute any known method for monitoring the intracellular localization of ribozymes, such as the FISH method of Bertrand, recognizing that it was an art-recognized equivalent known to be

useful for the same purpose. As noted in MPEP 2144.06, it is *prima facie* obvious to substitute art-recognized equivalents known to be useful for the same purpose in the absence of unexpected results. An ordinary artisan also would have recognized from the teachings of Bertrand that the disclosed FISH method was a faster and simpler method of determining the intracellular localization of the ribozyme-helicase conjugates, and therefore, would have been motivated to substitute this method for the Northern blotting method described by Taira. Furthermore, as noted in MPEP 2144.07, it is *prima facie* obvious to select a known material based on its suitability for the intended purpose in the absence of unexpected results. In this case, Bertrand taught that the disclosed FISH method was suitable for determining the intracellular localizaation of ribozymes (see Figure 5, pages 79-81, and page 87). Therefore, an ordinary artisan would have been motivated to use this method to determine the intracellular localization of the ribozyme conjugates of Taira with a reasonable expectation of success. Finally, regarding claim 32, an ordinary artisan would have been motivated to perform the fluorescence *in situ* detection step using a fluorescently labeled binding partner specific for any component of the helicase-ribozyme conjugate of Taira (*e.g.* the helicase portion). An ordinary artisan would have had a reasonable expectation of success in detecting the helicase portion of the conjugates, since Taira taught antibodies that specifically bound to the helicase (paragraph 63). Thus, the methods of claims 21 and 32 are *prima facie* obvious in view of the combined teachings of Taira, Daskis, Thompson, and Bertrand.

Response to Arguments

14. Applicant's arguments filed on September 4, 2009 that remain pertinent to the new grounds of rejection have been fully considered, but they were not persuasive.

In view of the claim amendments, Applicant's arguments filed on September 4, 2009 regarding the rejection of claims 1, 2, 5-7, 11, 13-16, 24-26, 31, 91, 126, 128, and 129 under 35 U.S.C. 102(b) as being anticipated by Cheng currently apply to claim 129. Applicant argues that the reference does not teach all of the elements of claim 129. In particular, Applicant argues that the plain language of the claim requires the step of "providing a conjugate comprising a nucleic acid tag molecule and a nucleic acid binding enzyme" to occur before the step of "contacting a nucleic acid polymer with the conjugate" (see pages 9-11). Applicant also argues that MPEP 2111.01 II, which was cited previously as providing support for the Examiner's interpretation of the claims, provides support for Applicant's position rather than the position taken by the Office (see page 10). Applicant further argues that the Examiner has acknowledged that the claimed method steps require a particular order, specifically in the Advisory action dated 11/4/08, and that the present interpretation of the claims is inconsistent with the position taken in the advisory action (page 10).

Applicant's arguments were not persuasive, because as discussed previously, the plain language of claim 129 does not exclude a method wherein the "providing" step and the "contacting" steps occur simultaneously, such as the method of Cheng, in which the providing and contacting step occur simultaneously upon UV irradiation of mixture comprising the reverse transcriptase, dT_{10} primer, and $rA_{12\text{-}18}$ template. It is also noted that claim 129 does not appear to require that the conjugate comprising a nucleic acid tag molecule and a nucleic acid binding

enzyme is covalently linked at the providing step. Rather, the language of claim 129 encompasses methods, such as the method disclosed by Cheng, in which the covalently linked conjugate is provided after the UV cross-linking step. It is noted that, in contrast to Applicant's arguments, the recitation of "a first step", "a second step", and "a third step" does not confer a particular order on the method steps. This is consistent with the guidance set forth in MPEP 2111.01 II, which has been discussed previously. Finally, regarding Applicant's arguments with respect to the statements contained in the Advisory Action dated 11/4/08, the Advisory Action dated 11/4/08 did not intend to convey that the only possible interpretation of the limitations added in the after-final response was that the claimed methods require conducting the method steps in the order argued by Applicant. The statements in the Advisory Action were only intended to indicate that the newly added limitations are an attempt to require a particular order of conducting the method steps, and therefore, they would require more than a cursory consideration. Since Applicant's arguments were not persuasive, claim 129 remains rejected under 35 U.S.C. 102(b) as being anticipated by Cheng.

In view of the claim amendments, Applicant's arguments filed on September 4, 2009 regarding the rejection of claims 1, 2, 5, 6, 9, 11-16, 24-27, 31, 91, 125, 126, 128, and 130 under 35 U.S.C. 102(e) as being anticipated by Taira and the rejection of claims 1, 2, 5, 6, 9, 11-16, 24-27, 31, 91, 125, 126, 128, and 130 under 35 U.S.C. 102(a) as being anticipated by Tahira currently apply to claim 91, which has been rejected under 35 U.S.C. 102(e) as being anticipated by Taira and under 35 U.S.C. 102(e) as being anticipated by Tahira. Applicant argues that neither reference teaches "determining the position of one or more conjugates when bound to the nucleic acid molecule" as required the amendment to claim 91 (see page 13).

This argument was not persuasive, because the broadest reasonable interpretation of the above recitation is not limited to methods in which the position of the conjugate is determined while the conjugate is physically bound to the nucleic acid molecule as argued by Applicant at page 13. The above recitation only requires the practitioner to identify the position on the nucleic acid molecule to which the conjugate binds. Therefore, the above recitation encompasses methods, such as those disclosed by Taira and Tahira, wherein the determination of the position of the conjugate when bound to the nucleic acid molecule is determined indirectly using a downstream method, such as the detection of cleavage products. Since Applicant's arguments were not persuasive, claim 91 remains rejected under 35 U.S.C. 102(e) as being anticipated by Taira and under 35 U.S.C. 102(a) as being anticipated by Tahira.

Applicant's arguments, see page 14, filed on September 4, 2009 remain pertinent to the new ground of rejection above, where claims 1, 2, 5, 6, 9, 11-13, 17, 24-31, 125, 126, 128, and 130 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Taira in view of Daskis as evidenced by Thompson. Applicant argues that the rejection is improper, because Taira provides no motivation or reasonable rationale to label the nucleic acid tag molecule (*i.e.* the ribozyme) or the nucleic acid polymer (*i.e.* the target mRNA), since the method is concerned with monitoring the downstream effects of binding of the disclosed conjugate to the mRNA target (see page 14).

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge

generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, as discussed previously and reiterated above, the ordinary artisan would have been motivated to label the nucleic acid tag molecule (*i.e.* the ribozyme) and the mRNA target molecule of Taira using the backbone-specific fluorescent intercalating agents taught by Daskis, in order to obtain a rapid, sensitive, environmentally friendly, safe, and homogeneous method for analyzing the binding between the ribozyme-helicase conjugates of Taira and their mRNA targets. It is noted that the methods disclosed by Taira are not limited to methods in which ribozyme cleavage products are monitored as Applicant's response appears to argue at page 13. The methods disclosed by Taira also include methods of detecting the localization of the conjugate in a cell (see, for example, page 11). In these methods, the ordinary artisan would have been motivated to apply the teachings of Daskis in order to obtain a simpler and more environmentally friendly method of detecting the localization of the conjugates. Also, the use of the fluorescent intercalators taught by Daskis would have resulted in a simpler and more environmentally friendly means of monitoring the ribozyme cleavage reactions disclosed by Taira by eliminating the need for radioactive labels (see, for example, paragraphs 156-157 of Taira).

In view of the claim amendments, Applicant's arguments filed on September 4, 2009 regarding the rejection of claims 19, 20, 22, 23, 33, 34, and 68 under 35 U.S.C. 103(a) as being unpatentable over Taira in view of Tegenfeldt currently apply to claims 19, 20, 33, 34, and 68, which have been rejected under 35 U.S.C. 103(a) as being unpatentable over Taira in view of Daskis and further in view of Thompson and further in view of Tegenfeldt. Applicant argues

that the ordinary artisan would not have been motivated to utilize the linear polymer analysis system of Tegenfeldt when practicing the method of Taira, because the method of Taira only analyzes hybridization patterns indirectly via the detection of cleavage products (see page 15).

This argument was not persuasive, because the ordinary artisan would have recognized from the combined teachings of the cited references that use of the linear polymer analysis system described by Tegenfeldt would permit real-time detection of the interaction of the binding of the fluorescently labeled helicase-ribozyme conjugates resulting from Taira the combined teachings of Taira, Daskis, and Thompson, and thereby, simplify the detection of binding between the helicase-ribozyme conjugate and the mRNA target by eliminating the need to additionally detect cleavage products to monitor the binding of the conjugates to known targets.

In view of the claim amendments, Applicant's arguments filed on September 4, 2009 regarding the rejection of claims 21-23 and 32 under 35 U.S.C. 103(a) as being unpatentable over Taira in view of Bertrand currently apply to claims 21 and 32, which have been rejected under 35 U.S.C. 103(a) as being unpatentable over Taira in view of Daskis and further in view of Thompson and further in view of Bertrand. Applicant argues that the combined teachings of the cited references do not suggest all of the limitations of the rejected claims. In particular, Applicant argues that the portions of Taira that describe Northern blotting only detect the presence and location of the disclosed ribozyme or ribozyme-helicase conjugates in cells and do not comprise detection of the target nucleic acid as required by the claims (pages 15-16).

This argument was not persuasive, because the method resulting from the combined teachings of the cited references would necessary include the presence of a target nucleic acid

polymer. Specifically, when substituting FISH as taught by Bertrand for the Northern blotting method described by Taira, at least some of the detected helicase-ribozyme conjugates will be hybridized to the target nucleic acid. Accordingly, the combined teachings of the cited references suggest all of the claimed limitations.

Applicant's arguments, see pages 11-12, regarding the rejection of claim 125 under 35 U.S.C. 102(b) as being anticipated by Fisher have been considered, but they are moot as the rejection has been withdrawn in view of the claim amendments.

Conclusion

15. No claims are currently allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANGELA BERTAGNA whose telephone number is (571)272-8291. The examiner can normally be reached on Monday – Friday, 7:30 – 4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Angela M Bertagna/
Examiner, Art Unit 1637

/GARY BENZION/
Supervisory Patent Examiner, Art Unit 1637